

# Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial

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**Study objective:** Nonsteroidal anti-inflammatory drugs are used extensively for the management of acute and chronic pain, with ketorolac tromethamine being one of the most frequently used parenteral analgesics in the emergency department (ED). The drugs may commonly be used at doses above their analgesic ceiling, offering no incremental analgesic advantage while potentially adding risk of harm. We evaluate the analgesic efficacy of 3 doses of intravenous ketorolac in ED patients with acute pain.

**Methods:** We conducted a randomized, double-blind trial to assess the analgesic efficacy of 3 doses of intravenous ketorolac (10, 15, and 30 mg) in patients aged 18 to 65 years and presenting to the ED with moderate to severe acute pain, defined by a numeric rating scale score greater than or equal to 5. We excluded patients with peptic ulcer disease, gastrointestinal hemorrhage, renal or hepatic insufficiency, allergies to nonsteroidal anti-inflammatory drugs, pregnancy or breastfeeding, systolic blood pressure less than 90 or greater than 180 mm Hg, and pulse rate less than 50 or greater than 150 beats/min. Primary outcome was pain reduction at 30 minutes. We recorded pain scores at baseline and up to 120 minutes. Intravenous morphine 0.1 mg/kg was administered as a rescue analgesic if subjects still desired additional pain medication at 30 minutes after the study drug was administered. Data analyses included mixed-model regression and ANOVA.

**Results:** We enrolled 240 subjects (80 in each dose group). At 30 minutes, substantial pain reduction was demonstrated without any differences between the groups (95% confidence intervals 4.5 to 5.7 for the 10-mg group, 4.5 to 5.6 for the 15-mg group, and 4.2 to 5.4 for the 30-mg group). The mean numeric rating scale pain scores at baseline were 7.7, 7.5, and 7.8 and improved to 5.1, 5.0, and 4.8, respectively, at 30 minutes. Rates of rescue analgesia were similar, and there were no serious adverse events. Secondary outcomes showed similar rates of adverse effects per group, of which the most common were dizziness, nausea, and headache.

**Conclusion:** Ketorolac has similar analgesic efficacy at intravenous doses of 10, 15, and 30 mg, showing that intravenous ketorolac administered at the analgesic ceiling dose (10 mg) provided effective pain relief to ED patients with moderate to severe pain without increased adverse effects. [Ann Emerg Med. 2016;■:1-8.]

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## INTRODUCTION

### Background

Ketorolac tromethamine is one of the most commonly used parenteral analgesics in the emergency department (ED) for the treatment of moderate to severe pain, alone or in combination with opioid analgesics.<sup>1</sup> It is a nonsteroidal anti-inflammatory drug that belongs to a group of nonopioid analgesics that primarily inhibit (reversibly) the activity of both cyclooxygenase-1 (constitutive) and cyclooxygenase-2

(inducible) enzymes and block the synthesis of prostaglandins and thromboxanes.<sup>2</sup> Ketorolac is available in oral, intranasal, and parenteral forms. It possesses significant analgesic and antipyretic properties, and it has been widely used to treat a variety of acute painful conditions. It has high cyclooxygenase-1 enzyme selectivity, has a half-life of 2.4 to 8.6 hours, and is extensively metabolized in the liver and eliminated through the kidneys.<sup>2</sup> Ketorolac has multiple drug-drug interactions, many of which arise from the reduction in glomerular filtration

**Editor's Capsule Summary***What is already known on this topic*

Despite known ceiling effects on nonsteroidal analgesia, many deploy enhanced singular doses, seeking better pain control.

*What question this study addressed*

Does increasing the dose of intravenous ketorolac improve analgesia in emergency department (ED) patients with a wide variety of pain syndromes?

*What this study adds to our knowledge*

In a single-site, controlled, randomized trial with 240 subjects, pain reduction at 30 minutes postdosing for 10, 15 and 30 mg of ketorolac was not different and adverse effects did not differ.

*How this is relevant to clinical practice*

There is no benefit to using higher doses of ketorolac for pain relief in unselected ED patients.

induced by ketorolac or by competitive displacement of the second drug from protein-binding sites. Coadministration of ketorolac with warfarin leads to worsening of gastrointestinal hemorrhage; with steroids, to peptic ulcer disease; with diuretics, to nephrotoxicity and hyperkalemia; and with lithium and digoxin, to toxicity of these agents.<sup>2,3</sup>

**Importance**

Nonsteroidal anti-inflammatory drugs may commonly be used at doses above their analgesic ceiling, although this may not offer an incremental analgesic advantage and potentially adds risk of harm. Analgesic ceiling is the dose of a drug beyond which any further dosage increase results in no additional analgesic effect.<sup>4</sup> The ketorolac analgesic ceiling dose of 10 mg is lower than both the dosing regimen recommended in emergency medicine textbooks<sup>5</sup> and the recommended Food and Drug Administration–approved doses: 30 mg intravenously and 60 mg intramuscularly for patients younger than 65 years.<sup>6</sup> Ketorolac is the only analgesic whose parenteral dosing is 3 to 6 times higher than the oral regimen based on the Food and Drug Administration–recommended oral regimen of 10 mg every 6 hours for no more than 5 days.<sup>6</sup>

Like all nonsteroidal anti-inflammatory drugs, ketorolac has several potentially serious adverse effects: gastrointestinal hemorrhage, nausea, vomiting, dyspepsia, dizziness or lightheadedness, and somnolence. Of these, gastrointestinal hemorrhage is the most concerning because

it also appears to be dose dependent. Of all nonsteroidal anti-inflammatory drugs, the risk of gastrointestinal hemorrhage is highest for ketorolac and increases with higher doses.<sup>7</sup> In healthy volunteers, single doses of parenteral ketorolac have been demonstrated to interfere with platelet function by prolonging bleeding time, inhibiting platelet aggregation, and reducing platelet thromboxane production.<sup>8-10</sup> Likewise, single doses of ketorolac at 15 and 30 mg intravenously and 60 mg intramuscularly have been shown to worsen hemorrhage in postoperative patients.<sup>11,12</sup>

Several studies have demonstrated that ketorolac analgesic efficacy at 10 mg is similar to that at higher doses (15 to 90 mg) for treatment of postoperative and cancer pain while minimizing the adverse effects typical of higher dosages.<sup>13-16</sup> Despite this, Food and Drug Administration recommendations and the majority of studies of parenteral ketorolac in the ED advocate the use of doses that are higher than 10 mg.

**Goals of This Investigation**

We hypothesized that the standard dosing of ketorolac is supra-analgesic and that higher doses are superfluous. We conducted a clinical trial comparing the analgesic efficacy of 3 doses of intravenous ketorolac for acute pain in the ED.

**MATERIALS AND METHODS****Study Design and Setting**

This was a randomized, double-blind trial to determine the analgesic equivalency of intravenous administration of ketorolac at 10 mg for the treatment of acute pain compared with higher doses of 15 and 30 mg.

We conducted this study at a 711-bed urban community teaching hospital with an annual ED census of greater than 120,000 visits. Patient screening, enrollment, and data collection were performed by study investigators (S.M., M.Y., I.P., R.H., J.D., and C.F.). The Maimonides Medical Center Institutional Review Board approved the trial. We report this trial in accordance with the Consolidated Standards of Reporting Trials statement.<sup>17</sup>

**Selection of Participants**

Patients considered for inclusion comprised adults aged 18 to 65 years who presented to the ED primarily for management of acute flank, abdominal, musculoskeletal, or headache pain with an intensity of 5 or greater on a standard 0 to 10 numeric rating scale and who would routinely be treated with intravenous ketorolac in our ED as determined by the treating attending emergency

physician. Acute pain is defined in our study as having an onset within 30 days or less. Exclusion criteria included older than 65 years, pregnancy or breastfeeding, active peptic ulcer disease, acute gastrointestinal hemorrhage, known history of renal or hepatic insufficiency, allergy to nonsteroidal anti-inflammatory drugs, unstable vital signs (systolic blood pressure <90 or >180 mm Hg; pulse rate <50 or >150 beats/min), and patients having already received analgesic medication. For the purposes of this study, intravenous ketorolac was used without coadministration of any other analgesics, with the exception of rescue medication.

Enrollment of patients occurred between March 2014 and December 2015. Screening and enrollment took place Monday through Friday, 8 AM to 8 PM, when an ED pharmacist was available for blinded medication preparation. Study investigators approached all potentially qualifying participants. All participants provided written informed consent and Health Insurance Portability and Accountability Act authorization. For non-English speakers, a language-appropriate consent form was used and noninvestigator, hospital-employed, trained interpreters assisted in acquisition of informed consent.

### Interventions

The on-duty ED pharmacist prepared 10-, 15-, or 30-mg doses of ketorolac in 10 mL of normal saline solution. Medications were prepared in identical syringes according to predetermined randomization generated in SPSS (version 20.0; SPSS, Inc., Chicago, IL) by the research manager. The research manager and statistician, who were independent of data collection, conducted the programming of the randomization list, confirmation of written consent acquisition, and statistical analyses. ED pharmacy investigators maintained the randomization list, prepared the medication, and delivered it to the nurse caring for the study participant in a blinded manner. Each dose of ketorolac was administered by intravenous push during 1 to 2 minutes. The preparing pharmacist, research manager, and statistician were the only ones with knowledge of the study arm to which the participant was randomized; providers, participants, and the data collecting research team were blind to the medication received. Study investigators consisted of 2 treating physicians, who assisted in screening and supervised the research fellow, and research coordinators, who enrolled patients and recorded pain scores, vital signs, and adverse effects at baseline and 15, 30, 60, 90, and 120 minutes. For subjects still desiring pain medication 30 minutes after study drug administration, investigators offered intravenous morphine at 0.1 mg/kg as a rescue analgesic.

### Outcome Measures

The primary outcome was reduction in numeric rating scale pain score at 30 minutes from medication administration. Secondary outcomes included rates and percentages of subjects experiencing adverse effects and requiring rescue analgesia.

### Primary Data Analysis

Research staff recorded all data on data sheets (separate from clinical data), entered them into Microsoft Excel (Microsoft, Redmond, WA), and then imported them into the programs used for statistical analysis. Data were described in terms of mean (SD) or 95% confidence limits in the case of normally distributed data and frequency (percentage) in the case of categorical data.

Data analysis of the pain data was based on the principle of intention to treat. To fulfill this requirement and to account for data missing because of dropout, multiple imputation (SAS Proc MI; SAS 9.4; SAS Inc, Cary, NC) was used to create 5 data sets wherein any missing pain datum was imputed with the Markov chain Monte Carlo method. In accordance with Biering et al,<sup>18</sup> an imputation model was run for each of the pain scores with missing data (ie, at 15, 30, 60, 90, and 120 minutes). At each time point ( $t_i$ ), the model consisted of the pain scores that were immediately before ( $t_{i-1}$ ) and immediately subsequent ( $t_{i+1}$ ), as well as factors that were related to whether a subject presented with a missing pain assessment. These factors included baseline pulse rate, chief complaints of flank pain or headache, and a diagnosis of renal colic. At baseline, no imputation was necessary because there were no missing pain assessments, whereas, for the final pain assessment at 120 minutes, the imputation model included only the preceding pain assessment at 90 minutes plus the factors related to missing pain assessments.

The imputed data sets were each analyzed with mixed-model linear regression to test for a significant group  $\times$  time interaction, which would have been an indication of the presence of a group difference in pain levels at 1 or more time points. The imputed data were also analyzed for the main effects of group and time. The results from each imputed data set were then analyzed and combined with the SAS macro `type3_MI_mixed`<sup>19</sup> to arrive at a single weighted test statistic and a *P* value.

Additional sensitivity analyses of the data were carried out in a similar fashion. Imputed data were reanalyzed with generalized linear modeling with an underlying  $\gamma$  function to account for possible skewness at later time points first, and then reanalyzed with ordinary least squares repeated-measures ANOVA. Finally, the per-protocol data, consisting only of subjects with complete measurements at

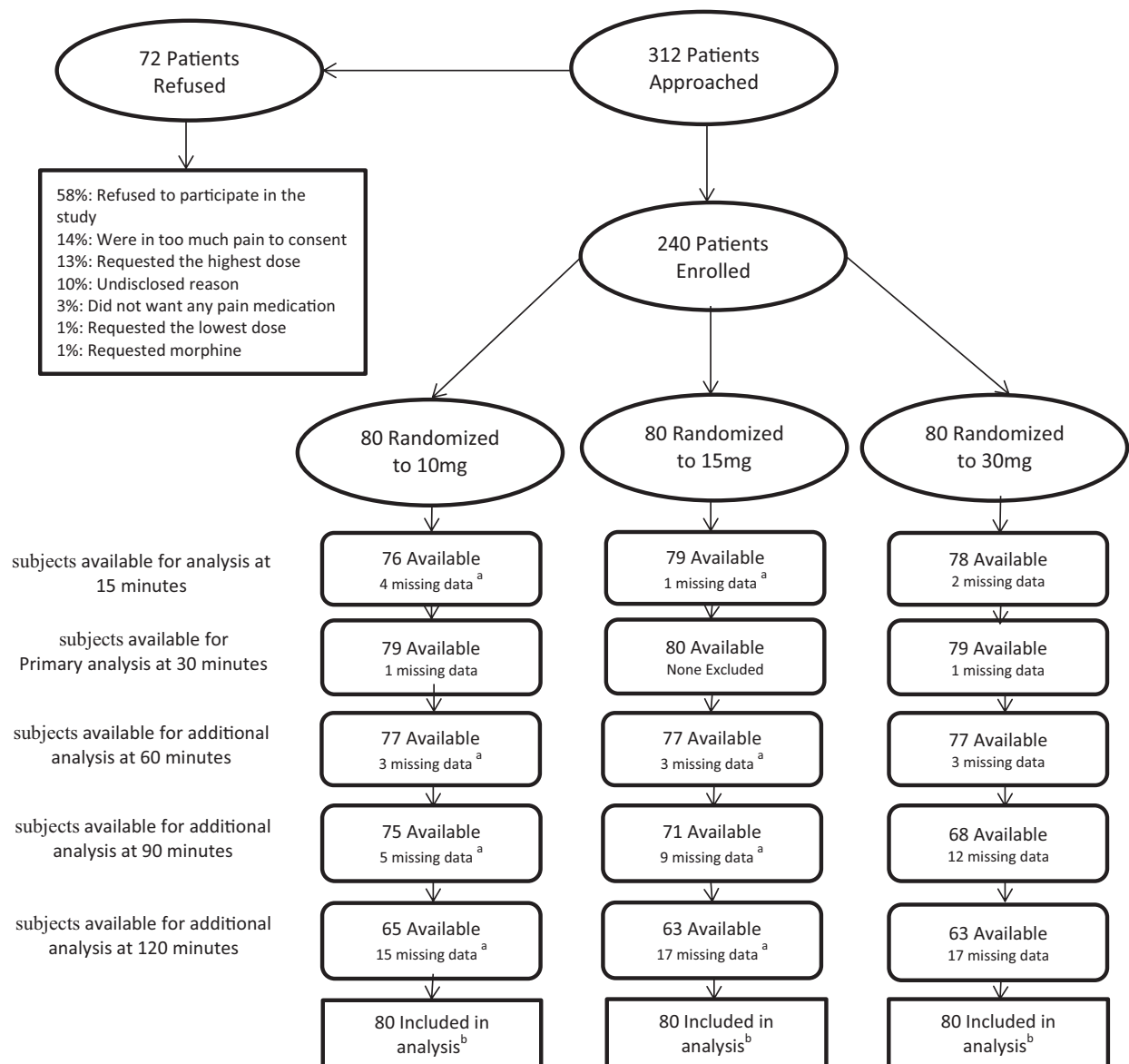
all time points, were analyzed with mixed-model linear regression and ordinary least squares repeated-measures ANOVA. All tests were 2 sided with a significance level of .05.

The main hypothesis was that there would be equivalence of dose effect across the 3 groups at every time point, and the primary comparison consisted of the pain assessment at 30 minutes. In accordance with Bijur<sup>20</sup> and Holdgate et al,<sup>21</sup> we assumed a minimal clinically significant difference of 1.3 between the 3 ketorolac groups at the 30-minute pain assessment and an SD of 3.0. A power analysis determined that a sample of 78 subjects per

group provided at least 80% power to detect a minimal clinically significant difference of at least 1.3 at 30 minutes with  $\alpha=.05$ .

## RESULTS

We enrolled 240 subjects (80 in each group for 10, 15, and 30 mg) in our study. The patient flow diagram is illustrated in Figure 1. During the study, instances of missing pain scores, vital signs, and adverse effects data occurred because of either a subject's absence from the ED for radiologic testing or discharge from the ED before data



<sup>a</sup>Subjects were missing data because of either discharge or transfer from the ED.

<sup>b</sup>Multiple imputation was used to account for missing data.

**Figure 1.** Study flow diagram for consented subjects.

**Table 1.** Baseline patient characteristics.

Characteristics	Group		
	Ketorolac 10 mg	Ketorolac 15 mg	Ketorolac 30 mg
No. of subjects	80	80	80
Age, mean (SD)	41.5 (12.1)	40.1 (12.1)	38.8 (11.6)
Male sex, frequency (%)	39 (48.8)	32 (40)	37 (46.3)
Pain, mean (SD)	7.73 (1.65)	7.54 (1.61)	7.80 (1.55)
<b>Chief complaints (%)</b>			
Abdominal	32 (40.0)	29 (36.3)	30 (37.5)
Flank	31 (38.8)	27 (33.8)	21 (26.3)
Musculoskeletal	16 (20.0)	21 (26.3)	20 (25.0)
Headache	1 (1.3)	3 (3.8)	9 (11.3)
<b>Blood pressure, mm Hg</b>			
Systolic	129.4 (17.0)	125.2 (20.3)	122.6 (21.1)
Diastolic	75.2 (11.4)	73.3 (12.4)	75.1 (14.2)
Pulse rate, beats/min	80.8 (15.2)	74.2 (13.6)	78.6 (15.8)
Respiratory rate, breaths/min	18.5 (3.3)	17.8 (2.5)	19 (8.4)
Oxygen saturation	98.3 (2.2)	98.8 (1.4)	99.1 (1.0)
<b>Duration of pain, h</b>			
Abdominal	62.6 (52)	41.5 (44)	63.2 (86)
Flank	69.0 (68)	36.8 (34)	54.6 (62)
Musculoskeletal	59.4 (60)	83.9 (110)	43.6 (44)
Headache	48.0*	40.7 (36)	85.6 (81)

\*Only 1 patient.

collection was completed. The groups were similar in terms of demographic characteristics and baseline vital signs (Table 1). Mean ages and sex were 41.5, 40.1, and 38.8 years and 39%, 32%, and 37% men, respectively. Baseline numeric rating scale pain scores were equivalently high in all 3 study groups (Table 2).

There were no differences in the pattern of missing pain assessments across the 3 groups. For the 10-mg group, 15.0% of the subjects had only 1 missing pain assessment, whereas 18.8% and 10.0% of the patients in the 15- and 30-mg groups, respectively, had only a single missing pain assessment; 6.3%, 6.3%, and 8.8% of patients in the 3 groups had 2 missing pain assessments, and 2.5%, 1.3%, and 6.3% had 3 missing pain assessments.

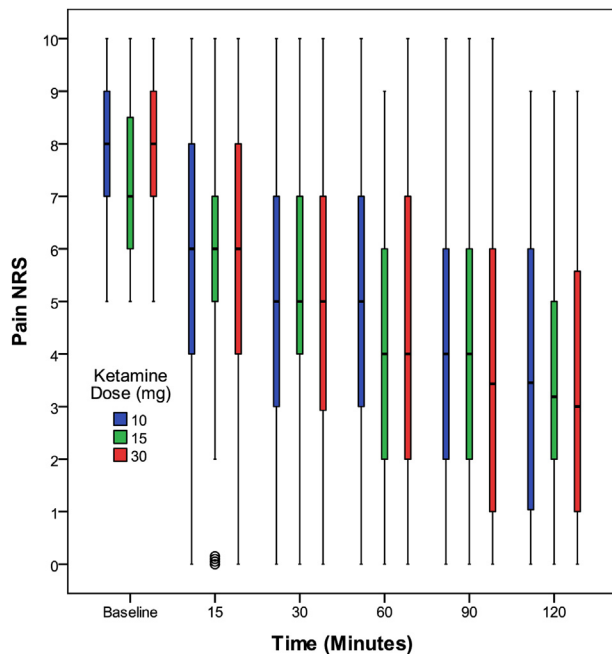
At 30 minutes postadministration, subjects randomized to receive 10 mg of intravenous ketorolac improved from a mean pain numeric rating scale score at baseline of 7.7 to a mean score of 5.2 (difference=2.5), the 15-mg group improved from 7.5 to 5.1 (difference=2.4), and the 30-mg group improved from 7.8 to 4.8 (difference=3.0). Reductions in pain scores from baseline to 30 minutes were statistically significant for all subjects. However, there were no differences in pain score reduction from baseline to 30 minutes across the 3 dose groups. Likewise, we observed no differences in the mean numeric rating scale pain scores themselves between dose groups at 30 minutes. The 95% confidence intervals for the ketorolac groups were similar: 4.6 to 5.8 for the 10-mg group, 4.5 to 5.6 for the 15-mg group, and 4.2 to 5.4 for the 30-mg group.

All subjects showed reductions in mean numeric rating scale pain scores relative to baseline at all subsequent time points (15 to 120 minutes). Moreover, as shown in Table 2, subjects' reported pain scores at each time point were similar in all 3 groups, with marginal differences in 95% confidence intervals in comparison of imputed and nonimputed data (ie, per protocol). As shown in Figure 2,

**Table 2.** Nonimputed and imputed pain scores for the 10-, 15-, and 30-mg ketorolac dose groups over time.

Time	Ketorolac Dose, mg	Nonimputed		Imputed	
		Mean (SD)	95% Confidence Interval for Mean	Mean (SD)	95% Confidence Interval for Mean
Baseline	10	7.73 (1.65)	7.36–8.09	7.73 (1.65)	7.36–8.09
	15	7.54 (1.61)	7.18–7.90	7.54 (1.61)	7.18–7.90
	30	7.80 (1.55)	7.46–8.14	7.80 (1.55)	7.46–8.14
15 min	10	6.12 (2.45)	5.56–6.68	6.04 (2.50)	5.48–6.59
	15	5.73 (2.43)	5.19–6.28	5.76 (2.43)	5.22–6.30
	30	5.94 (2.54)	5.36–6.51	5.87 (2.54)	5.31–6.44
30 min	10	5.13 (2.71)	4.52–5.73	5.14 (2.70)	4.54–5.74
	15	5.05 (2.56)	4.48–5.62	5.05 (2.56)	4.48–5.62
	30	4.84 (2.86)	4.19–5.48	4.81 (2.85)	4.18–5.45
60 min	10	4.56 (2.77)	3.93–5.19	4.60 (2.74)	3.99–5.21
	15	4.09 (2.61)	3.50–4.68	4.11 (2.58)	3.53–4.68
	30	4.11 (2.93)	3.43–4.78	4.14 (2.87)	3.50–4.78
90 min	10	4.03 (2.67)	3.41–4.64	4.09 (2.68)	3.50–4.69
	15	3.92 (2.60)	3.31–4.53	3.84 (2.54)	3.28–4.41
	30	3.66 (3.02)	2.93–4.39	3.56 (2.84)	2.93–4.19
120 min	10	3.77 (2.96)	3.04–4.50	3.74 (2.73)	3.13–4.35
	15	3.60 (2.37)	3.01–4.20	3.54 (2.26)	3.03–4.04
	30	3.44 (3.00)	2.69–4.20	3.46 (2.78)	2.85–4.08





**Figure 2.** Box-plots for reported pain NRS comparing dose groups over time.

the box plots at each time point underscore the similarity in pain ratings across the 3 study groups. Likewise, all results from the sensitivity analyses provided support for the hypothesis of equivalent pain reduction across the 3 doses of ketorolac, with no group $\times$ time interaction effects.

All of the subjects who reported complete resolution of pain were treated solely with the study medication, without use of a rescue analgesic dose of morphine. There were no differences between the groups with respect to use of rescue morphine analgesia at any time (Table 3).

There were no clinically concerning changes in vital signs and no clinically significant adverse effects related to the study medication at any dose. The most commonly reported adverse effects were dizziness, nausea, and headache, with no differences across the 3 doses (Table 4).

**Table 3.** Rate of rescue morphine over time by number of patients per group.

Time, Minutes	10 mg (%)	15 mg (%)	30 mg (%)
15	0	0	0
30	4 (5.0)* <sup>†</sup>	3 (3.8)	4 (5.0)
60	4 (5.2)	7 (9.0)	4 (5.3)
90	7 (9.3)	4 (5.5)	7 (10.3)
120	3 (4.6)	8 (12.7)	2 (3.2)

\*Frequency (percentage).

<sup>†</sup>Denominators are all based on the number of patients available at each time point per group.

**Table 4.** Common adverse effects across the 3 ketorolac dose groups.

Adverse Effects	Ketorolac Group (%)		
	10 mg	15 mg	30 mg
Dizziness	14 (17.5)	16 (20.0)	12 (15.0)
Nausea	9 (11.3)	11 (13.8)	8 (10.0)
Headache	8 (10.0)	2 (2.5)	3 (3.8)
Itching	0	1 (1.3)	1 (1.3)
Flushing	0	1 (1.3)	0

## LIMITATIONS

This was a single-center study in which subjects were enrolled as a convenience sample according to availability of members of both the research and pharmacy teams. This may have led to selection bias or underrepresentation of patients who may present to the ED late at night.

Instances of missing data occurred (vital signs, pain score, and adverse effects) because of subjects being discharged or being out of the ED for radiologic imaging, and that may have introduced bias. Our stringent exclusion criteria and sample size of 240 subjects were inadequate to assess variance in safety of the 3 different doses of study medication. The study duration was inadequate to compare the different doses with respect to their adverse effect profiles such as gastrointestinal bleeding and renal impairment because there was lack of follow-up after 120 minutes after study drug administration and after discharge. Our study did not assess whether higher doses may have resulted in prolonged pain relief beyond the 120-minute mark.

## DISCUSSION

Ketorolac is widely administered for pain management in a variety of inpatient and outpatient settings worldwide. Parenteral ketorolac has demonstrated analgesic efficacy similar to that for opioids in patients with cancer and postoperative pain.<sup>13,14,22</sup> In the ED setting, ketorolac is one of the most commonly administered parenteral analgesics and is used for a wide variety of pain causes, including musculoskeletal pain, renal colic, and headache.<sup>1,23,24</sup> Safdar et al<sup>25</sup> showed that combining morphine and ketorolac for renal colic yielded pain relief superior to that of either drug alone and was also associated with decreased requirement for rescue analgesia.

Ketorolac dosing regimens vary widely. In unpublished data examining nearly 50,000 administrations of ketorolac during 10 years in our ED, we found large variations of dosing patterns, from 10 to 60 mg (unpublished data). In addition, a number of published trials have also compared different ketorolac dosing regimens. Reuben et al<sup>13</sup>

demonstrated that smaller doses of ketorolac (7.5 mg every 6 hours) had a morphine-sparing effect equivalent to that of larger doses (10, 12.5, 15, or 30 mg) in patients who had undergone spinal fusion surgery. In a similar study, Brown et al<sup>16</sup> found no statistically significant differences in pain relief between 3 groups of patients randomized to receive intravenous ketorolac (10 versus 30 mg) or 4 mg of intravenous morphine to treat postoperative pain. Minotti et al<sup>15</sup> found no difference in cancer pain relief between intramuscular ketorolac at 10 and 30 mg and diclofenac at 75 mg. Staquet<sup>14</sup> also found no difference in pain relief for cancer patients when using 10-, 30-, or 90-mg doses of intramuscular ketorolac.

These studies strongly suggest that ketorolac has an analgesic ceiling dose of 10 mg and that increasing the dose fails to provide additional analgesic relief. Other published investigations have shown that ketorolac's adverse effects seem to be dose related<sup>3</sup> and that single doses can impair platelet function and worsen postoperative hemorrhage.<sup>8-12</sup>

Our findings parallel those of other research. Neighbor and Puntillo<sup>26</sup> found that 9% to 10% of patients who received either intramuscular ketorolac or oral ibuprofen experienced an adverse effect of nausea or gastrointestinal upset, dizziness or lightheadedness, sleepiness, and headache. Similar results occurred in the study by Brown et al,<sup>16</sup> in which 17% (5/30) of the ketorolac 10-mg group and 28% (8/32) of the 30-mg group reported nausea as the most common adverse effect.

Our study differs from previously published investigations in several important ways. Minotti et al<sup>15</sup> and Staquet<sup>14</sup> used intramuscular ketorolac regimens, whereas our patients received ketorolac intravenously. The study by Minotti et al<sup>15</sup> used the visual analog scale (0 to 100 mm) and the study by Brown et al<sup>16</sup> used a 4-point pain scale, whereas we used a numeric rating scale to quantify pain levels. Because it is more feasible in an ED setting to ask patients to rate their pain on a scale of 1 to 10 than to find a visual analog scale line, a numeric rating scale reliably addressed the need to assess and follow changes in our subjects' pain scores.<sup>20</sup> Ultimately, although others studied subjects with cancer pain or postoperative pain, our subjects had pain from diverse causes, reflecting a broader population of ED patients who currently receive ketorolac.

In summary, ketorolac has similar analgesic efficacy profiles at intravenous doses of 10, 15, and 30 mg for short-term treatment of acute moderate to severe pain in the ED. The results of our study provide a basis for changes in practice patterns and guidelines in ED care, supporting use of the 10-mg intravenous ketorolac dose.

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*Author contributions:* SM and CF conceived the study, designed the trial, obtained research funding, and supervised the conduct of the trial and data collection. SM, MY, IP, RH, JD, and CF undertook recruitment of participating subjects and managed the data, including quality control. AL and PH provided statistical advice on study design and analyzed the data. AL chaired the data oversight committee. MY and JD drafted the article and all authors contributed substantially to its revision. AL and PH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SM takes responsibility for the paper as a whole.

All authors attest to meeting the four [ICMJE.org](http://www.icmje.org) authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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